
Harvard University Commencement Address

Harold Varmus, Director, NIH

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Mr. President, alumni, graduates, parents, friends:

Many members of today's graduating class reacted to the news that I would give this year's Commencement Address, just as I did: with surprise. The Harvard Crimson recorded some undergraduate responses: "Who is he?" "Wow, that's boring. Everyone else got someone exciting." Editorials criticized the process by which "Dr. Who" was selected. I was featured in entertaining cartoons, something that hasn't happened during three years in Washington. I may never be this famous again.

There is an advantage to starting from low expectations. Agreed, I am not running for President, and I am not a prime minister or a general. But I speak for an element of our culture at least as important as politics or war---an element that has not been at this podium since Alexander Fleming, the discoverer of penicillin, addressed the graduating class of 1945. That element is science.

The products of science shape and pervade our lives. Sir Francis Bacon made this point in 1620. "Printing, gunpowder, and the magnet," he wrote, "have changed the whole face and state of things throughout the world....no empire, no sect, no star seems to have exerted greater power and influence in human affairs." Modern equivalents are legion: consider e-mail, nuclear weapons, biotechnology.

I will speak today about the effects of science on our lives. But I will also emphasize science in its most fundamental form, the process by which we make discoveries about the world---like the atom or the gene--- that precede practical inventions. At its core, science is a way of thinking---making judgments, often creative ones, that are based on evidence, not on desires, received beliefs, or hearsay. Thinking in this way is not unique to the natural sciences; it is important for many disciplines. But the pursuit of evidence, through experiment and observation, is the lifeblood of science.

My own brand of science is biology---more specifically, biology linked to medicine. I was not born a scientist. In my youth, I preferred tennis and novels to chemistry sets. My father, Harvard Class of '28, was a physician, so medical topics were often at the dinnertable. Like my friends, I grew up listening to parental concerns about polio, the crippling illness then common among children and famous for afflicting our family hero, Franklin Delano Roosevelt. In summertime, public swimming pools were forbidden. Neighborhood kids nearly died of the disease. For my generation, the announcement of an effective polio vaccine was a landmark. For us, the recent eradication of naturally acquired polio from this hemisphere still seems unbelievable.

When I was fourteen, and Jonas Salk had just achieved fame for the first polio vaccine, my parents taught me an important lesson about how progress occurs in medical research. I had intended to describe Salk's triumph in a public

speaking contest (a contest, which, incidentally, I did not win). But they persuaded me to talk instead about John Franklin Enders. A member of the Harvard Medical School faculty, Enders and two younger colleagues had been the first to grow the polio virus abundantly, by infecting animal cells in laboratory flasks. Previously, virus was prepared with difficulty, mainly from the brains of infected primates. Enders' discovery was pivotal, because Salk needed to inactivate vast amounts of poliovirus for use in a vaccine. Making and testing vaccines ---Salk's and later Sabin's--- came to seem less stirring to me than the more subtle triumph of learning how to grow the virus. And Enders became a heroic figure for me, even before I knew about his long path to science--- studying English literature at your graduate school and converting to microbiology at nearly thirty.

I too had trouble settling on a career. While my fellow pre-meds worked late in their labs, I was editing the Amherst College paper and writing about Charles Dickens. In a prolonged adolescence as a Harvard graduate student, I read Beowulf, Shakespeare, and Sir Thomas Browne, and listened to Bill Alfred, Harry Levin, and Anne Ferry. Finally I went to medical school---in part, because someone once told Gertrude Stein that it "opened all doors," in part because medical students seemed more eager than I was to get out of bed in the morning.

Like many physician-scientists of my generation, I learned to do and to love research while working at the National Institutes of Health, the Federal agency that supports most of the basic medical research in this country. I arrived at the NIH as a twenty-eight year-old doctor seeking two things: the credentials to become a medical school professor and an alternative to service in Vietnam. Then, one day some months later, I was abruptly transformed into a committed scientist, when a method I was developing to detect expression of a gene suddenly worked. The technique was not especially novel, and the questions I was asking were of interest only to a few people in the world. But, at that moment, I knew the intoxicating power of measurement and the sweet anticipation of my own results.

For more than twenty years afterwards, at the University of California in San Francisco, I enjoyed many measurements and many results. Despite the common myths about science, it was not lonely work. Much of the pleasure came from companionship---with my colleague, Mike Bishop---a newly-minted Harvard Overseer---and our students, post-docs, and technicians. Most of our experiments lacked discernable practical goals. We followed our hunches, working with cancer viruses from chickens and mice, supported largely by grants from the NIH. Eventually, over many years, patterns emerged. We had learned that cancer genes in viruses are derived from normal cellular genes---some of the genes that guide our growth and development. These genes, now called oncogenes, undergo the mutations that are the defining events in cancer. Obscure viruses from experimental animals had in this way allowed us to touch directly the heart of human cancer. A path to understanding had been opened.

Like researchers in all fields, I have also known disappointment, boredom, surprise, and even irony. One example was especially instructive. The painful reality of cancer has always loomed in the background of my work, because my mother and her mother died of breast cancer. For this reason, for many years my lab studied a virus that causes breast cancer in mice, in hopes of finding relatives of human breast cancer genes. Ultimately, we discovered interesting genes that guide formation of the brain and other organs. But, in this case, they don't appear to be involved in human cancer of any kind. There is no simple road map for this kind of research.

In 1989, our discovery of oncogenes was publicly recognized with the award of a Nobel Prize. Four years later, when President Clinton and Secretary Shalala invited me to become the Director of the NIH, I could hardly say no. My indebtedness was deep. The chance to repay it with public service has been gratifying.

This new job has given me a deeper appreciation of the measured pace of progress in medical research. Every morning, on the way to my office, I cross the portico from which Franklin Roosevelt dedicated the first NIH buildings on a late fall day in 1940. His paralyzed legs braced with metal, his energies worn down by his third Presidential campaign, his mind focused on the World War already being waged in Europe, FDR made a powerful statement about medical research:

"The total defense, which this Nation seeks, [he said] involves a great deal more than building airplanes, ships, guns

and bombs. We cannot be a strong Nation unless we are a healthy Nation. And so we must recruit not only men and materials but also knowledge and science in the service of national strength."

Roosevelt's optimism about medical research seems, in retrospect, amazing. Doctors could not prevent or treat the poliovirus infection that had paralyzed him nearly twenty years earlier. John Franklin Enders and vaccines were still in the future; the main therapies were iron lungs and warm baths. Most of the staples of modern medicine were also still unknown. Antibiotics. Hormone replacements. Effective drug therapies for psychotic illnesses. Pre-natal testing. Coronary bypass surgery and artificial joints. Also in the future were medications that could have lowered FDR's blood pressure and perhaps forestalled the stroke that killed him less than five years later, at the now relatively young age of sixty three.

Still, FDR's optimism proved to be justified. Even before the War was over, the chemical synthesis of quinine improved treatment of malaria for soldiers in the Pacific, and the manufacturing of Fleming's penicillin effectively controlled wound infections for the first time in the history of warfare. Following the War, inspired by these successes, the Federal government made unprecedented investments in many fields of science, through the NIH and other agencies. These investments have been essential for the vitality of American science ever since.

Polio vaccines and other early successes that encouraged public enthusiasm for research are now the stuff of legends. Let's consider a more recent and less famous success that gives a different perspective on the pace of progress. About two months ago, as I began to worry about this talk, the senior Senator from Massachusetts, a member of the Harvard Class of 1956 and of our Senate authorizing committee, paid a visit to the NIH. He and I were sitting on a pediatric ward in our research hospital in Bethesda, listening to a 27 year old blind man who looked like a skinny 8 year old boy. The patient was born with a disease called cystinosis, having inherited one damaged gene from each parent. In this very rare condition, the amino acid cystine cannot be removed from small sacs within his cells. As a result, cystine accumulates and forms crystals in those sacs, damaging the kidneys, eyes, and other tissues.

The patient told us how he was rescued from death by a kidney transplant at the age of 10, gradually lost his vision, and has lived with chronic pain. Senator Kennedy asked whether he had brothers and sisters. The patient replied, quite matter-of-factly, that two older brothers had died from the disease when he was very young, because kidney transplants were not yet available. So he felt fortunate to have been born recently enough to benefit from a life-saving transplant---the procedure pioneered by the Harvard surgeon, Joseph Murray (who, as it happens, spoke to the Medical School graduates today). The patient was also glad that affected children born yet more recently could avoid the kidney disease altogether; a recently-developed medication prevents formation of the crystals. A few minutes later a normal looking, eleven year old boy who had inherited the same disorder bounded into the room and spoke animatedly about sports, hobbies, school---and about the unpleasant taste of the medicine he had been taking nearly all his life.

This episode embodies many of my messages today: the message that science can improve lives in ways that are elegant in design and moving in practice; that the Federal government, much maligned in current politics, can be a powerful force for public benefit; that the government can work productively with universities, where the cellular defect in cystinosis was studied, and with industries, where the new drug was manufactured; and, finally, that progress in medical science occurs at a pace that may seem slow at the time to desperate parents, but astoundingly rapid in retrospect. Just consider: in the space of a generation, this lethal disease was made survivable with transplants, then curable with drugs.

Despite such triumphs, we have a long way to go. Yes, we can treat cystinosis and a few other genetic diseases, but there are thousands of inherited conditions we do not even understand. Yes, we have controlled polio and smallpox, but we are now struggling around the world with a new and intractable virus, HIV, and worried about invasions by exotic viruses, like Ebola and Lassa Fever. Yes, we can treat most bacterial infections with penicillin and other antibiotics, but many bacteria have now become resistant to what were once our most effective drugs. Yes, we have dramatically reduced the death rates for heart attacks and strokes, but we are still seeking ways to repair the hearts

and brains damaged by poor blood flow. Yes, we know the mutant genes responsible for many cancers, but we haven't transformed that knowledge into better therapies. Yes, we have improved the well-being of most people in the industrialized countries, but malaria, childhood diarrhea, and tuberculosis are still common in the developing world. And, yes, we have extended the average life span in this country to nearly eighty years, but we have made little progress against the maladies that make advanced age intolerable for so many people.

Old age and its illnesses are deepening concerns to all of us in this audience---even to youthful graduates. When Alexander Fleming spoke here 51 years ago, only one in seven graduates could expect to reach the age of 85. By conservative estimates, nearly half of you will live past that age. Today, less than four million Americans are over 85; when some of you reach 85, there will be about 20 million. This is not just good news. Today the government spends \$25 billion each year on medical care for this group alone. Multiply that by five. Add on the costs of care for the much larger group between 65 and 85. Without more public revenues from taxes, there will be little or no money left for other things the government buys, including the scientific research that might help. Clearly, if science cannot soon relieve the disorders of aging, we will confront some impossible choices.

Of all these disorders, the one we fear most is Alzheimer's Disease. We are right to fear it. It is a modern polio, and more. It destroys the brain and the personality. Its victims become a burden to spouses and children. Unlike polio, once common and now eradicated, or cystinosis, rare and now curable, Alzheimer's Disease is both untreatable and common. Unless things change, nearly half of us who reach the age of 85 will have signs of the disease.

Until recently, all we knew about Alzheimer's Disease was the ugly appearance of brain slices under the microscope and the unremitting deterioration of mental function. Traditional methods---chemistry and enzymology, microbiology and immunology, so successful in approaching polio and cystinosis---provided few clues.

Hope is coming from a new direction. One day about ten years ago, a middleaged Massachusetts man in the early stages of Alzheimer's Disease sought help from Dr. Daniel Pollen, a neurologist at the University of Massachusetts. His was not the most common form of the disease---the onset was early, and his relatives had been affected early too. With the help of the patient's family, Dr. Pollen reconstructed the family lineage and traced the disease back to one woman, named Hannah, born one hundred and fifty years ago in a Byelorussian village. Scientists here at Harvard, at the NIH, in Canada, and several other places, have tracked several inherited forms of Alzheimer's Disease to abnormal versions of single genes. These genes have been isolated in pure form, and we know the proteins they encode.

So an obvious question: How do we get from Hannah's gene to a remedy for Alzheimer's Disease? This, of course, is precisely what I can't tell you. I can't even tell you how to proceed. All I can do is predict the pace and flavor of the first moments. I imagine a brilliant young neuroscientist, our new Enders, who is trying to understand cell survival---perhaps studying a hormone that keeps nerve cells alive in a dish. One of her students, working late, suggests a novel interaction between the hormone and the protein made from Hannah's gene. The results are surprising, but reproducible. Someone in a lab thousands of miles away learns about this experiment and tries it in a different way, perhaps in a mouse model, and gets an even more interesting result. A young Salk, seeking an anti-Alzheimer drug at a biotechnology company, tries to block the interaction. We are on our way.

What do we need to make these things happen? New talent. Enthusiasm for science. Money. Strong institutions.

In that speech from the NIH steps on the eve of World War Two, FDR knew what we needed:

"All of us are grateful [he said] that we in the United States can still turn our thoughts and our attention to those institutions of our country which symbolize peace---institutions whose purpose it is to save life and not to destroy it."

FDR's confidence then underscores the dilemmas that now plague us in the aftermath of the Cold War. The Federal

government is broke and under attack by its own citizens. Other countries have recently surpassed our rate of spending for basic research. Universities and colleges are more strapped for funds than ever before. And many industries are turning away from research investments.

Dr. Who is not the person who can solve these problems. Instead I hope to recruit you to my passions. That our institutions must be fit to nurture talent. That new talent is essential to advance science. And that science, a source of beauty and delight, is also our best hope for fighting the threats of Alzheimer's and many other diseases.

Several hundreds of you graduating today have already enlisted to fight these battles, as future scientists or physicians. But the battle does not engage only those on the front lines. It will affect all of you. As worried patients, parents, and caretakers of parents. As taxpayers and good citizens of the world. And as thoughtful Harvard graduates, who know that science---like "no empire, no sect, no star"--- can eventually change "the whole face and state of things throughout the world."

Congratulations to you and good luck.

**COMMENCEMENT ADDRESS
HARVARD UNIVERSITY
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